Complete Summary

GUIDELINE TITLE

Methylphenidate poisoning: an evidence-based consensus guideline for out-of-hospital management.

BIBLIOGRAPHIC SOURCE(S)

Scharman EJ, Erdman AR, Cobaugh DJ, Olson KR, Woolf AD, Caravati EM, Chyka PA, Booze LL, Manoguerra AS, Nelson LS, Christianson G, Troutman WG, American Association of Poison Control Centers. Methylphenidate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007 Oct-Nov;45(7):737-52. [80 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Methylphenidate poisoning

Note:

- This guideline applies to ingestion of methylphenidate alone. Ingestion of additional substances could require different referral and management recommendations depending on the combined toxicities of the substances.
- This review focuses on the ingestion of more than a single therapeutic dose and the effects of an overdose. Although therapeutic use of methylphenidate

can sometimes cause adverse effects in adults and children—some idiosyncratic and some dose-dependent—these cases are not considered.

GUIDELINE CATEGORY

Evaluation
Management
Risk Assessment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Internal Medicine
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Emergency Medical Technicians/Paramedics
Nurses
Pharmacists
Physicians

GUIDELINE OBJECTIVE(S)

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial out-of-hospital management of patients with suspected ingestions of methylphenidate by:

- Describing the process by which a specialist in poison information should evaluate an exposure to methylphenidate
- Identifying the key decision elements in managing cases of methylphenidate ingestion
- Providing clear and practical recommendations that reflect the current state of knowledge
- Identifying needs for research

TARGET POPULATION

Children and adults with suspected methylphenidate poisoning

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Assessment of key decision elements for triage
    - Patient intent
    - Dose and formulation
    - Presence of symptoms

- Time of ingestion and presence of co-ingestants

Management

1. Referral to an emergency department
2. Pre-hospital activated charcoal administration by health professionals
3. Benzodiazepines administered by emergency medical service (EMS) personnel
4. Standard advanced cardiac life support (ACLS) measures administered by EMS personnel
5. Home observation
6. Follow-up

Note: Emesis induction for oral exposure was considered but not recommended.

MAJOR OUTCOMES CONSIDERED

- Signs and symptoms of toxicity
- Mortality
- Toxic dose

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Search Strategy

Literature searches for relevant articles were performed by a single investigator. The National Library of Medicine's PubMed database was searched (through March 2006) using methylphenidate as a Medical Subject Headings (MeSH) term with the subheadings poisoning (po) or toxicity (to), limited to humans. The PubMed database was further searched using methylphenidate as a textword (title, abstract, MeSH term, CAS registry) plus either poison* or overdos* or intox*, or toxic* limited to humans. This process was repeated in International Pharmaceutical Abstracts (1970–March 2006, excluding abstracts of meeting presentations), Science Citation Index (1977–March 2006), Database of Abstracts of Reviews of Effects (accessed March 2006), Cochrane Database of Systematic Reviews (accessed March 2006), and Cochrane Central Register of Controlled Trials (accessed March 2006). Reactions (1980–March 2006), the methylphenidate poisoning management in Poisindex, and the bibliographies of recovered articles were reviewed to identify previously undiscovered articles. Furthermore, North American Congress of Clinical Toxicology (NACCT) abstracts published in the Journal of Toxicology Clinical Toxicology (1995–2004) and Clinical Toxicology (2005) were reviewed for original human data.

Five major toxicology textbooks were reviewed for recommendations on the management of methylphenidate poisonings and for citations of additional articles with original human data in the chapter bibliographies. The Toxic Exposure Surveillance System (TESS) maintained by the American Association of Poison Control Centers was searched for deaths resulting from unintentional methylphenidate poisoning. These cases were abstracted for review by panel members. All United States poison control centers were surveyed in 2006 to ascertain their out-of-hospital management and triage practices for methylphenidate poisonings.

Criteria Used to Identify Applicable Studies

The recovered citations were entered into an EndNote library and duplicate entries were eliminated. The abstracts of these articles were reviewed, searching specifically for those that dealt with estimations of doses with or without subsequent signs or symptoms of toxicity and management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). Articles that did not meet either of the preceding criteria, did not add new data (e.g., reviews, editorials), or that exclusively described inpatient-only procedures (e.g., dialysis) were excluded.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level of Evidence	Description of Study Design
1a	Systematic review (with homogeneity) of randomized clinical trials
1b	Individual randomized clinical trials (with narrow confidence interval)
1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.)
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality randomized clinical trial)
2c	"Outcomes" research
3a	Systemic review (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case series, single case reports (and poor quality cohort and case control studies)
5	Expert opinion without explicit critical appraisal or based on physiology or bench research

Level of Evidence	Description of Study Design
6	Abstracts

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data Extraction Process

All articles that were retrieved from the original search were reviewed by a single trained physician abstractor. The complete papers were reviewed for original human data regarding the toxic effects of methylphenidate or original human data directly relevant to the out-of-hospital management of patients with methylphenidate toxicity or overdose. Relevant data (e.g., dose, effects, time of onset of effects, therapeutic interventions or decontamination measures provided, efficacy or results of any interventions, and overall patient outcome) were compiled into a table and a brief description of each article was written. This evidence table is available at http://www.aapcc.org/DiscGuidelines/methylphenidate%20evidencetable%20200 6-7-4.pdf.

The table of all abstracted articles was then forwarded to the panel members for review and consideration in developing the guideline. Efforts were made to locate foreign language articles and have their crucial information extracted, translated, and tabulated. A written summary of the data was created and distributed by the abstractor. Copies of all of the abstracted articles were made available for reading by the panel members on a secure American Association of Poison Control Centers (AAPCC) website.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

An expert consensus panel was established to develop the guideline (see Appendix 1 of the original guideline document). The American Association of Poison Control Centers (AAPCC), the American Academy of Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT) appointed members of their organizations to serve as panel members. To serve on the expert consensus panel, an individual had to have an exceptional record in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant US poison control center experience, and be an opinion leader with broad esteem. Two specialists in poison information were included as full panel members to provide the viewpoint of the end-users of the guideline.

Guideline Writing and Review

A draft guideline was prepared by the lead author. The draft was submitted to the expert consensus panel for comment. Using a modified Delphi process, comments from the expert consensus panel members were collected, copied into a table of comments, and submitted to the lead author for response. The lead author responded to each comment in the table and, when appropriate, the guideline draft was modified to incorporate changes suggested by the panel. The revised guideline draft was again reviewed by the panel and, if there was no strong objection by any panelist to any of the changes made by the lead author, the draft was prepared for the external review process.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The rating scheme for the strength of the recommendation (A-D, Z) is directly tied to the level of evidence supporting the recommendation.

Grade of Recommendation	Level of Evidence
A	1a
	1b
	1c
B	2a
	2b
	2c
	3a
	3b
C	4
D	5
Z	6

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External review of the second draft was conducted by distributing it electronically to American Association of Poison Control Centers (AAPCC), American Academy of Clinical Toxicology (AACT), and American College of Medical Toxicology (ACMT) members and the secondary review panel. The secondary review panel consisted of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (see Appendix 3 in the original guideline document). Comments were submitted via a

discussion thread on the AAPCC web site or privately through email communication to AAPCC staff. All submitted comments were rendered anonymous, copied into a table of comments, and reviewed by the expert consensus panel and the lead author. The lead author responded to each comment in the table and her responses and subsequent changes in the guideline were reviewed and accepted by the panel. Following a meeting of the expert consensus panel, the final revision of the guideline was prepared.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Grades of recommendation (A-D, Z) and levels of evidence (1a-6) are defined at the end of the "Major Recommendations" field.

1. All patients with suicidal intent, intentional abuse, or in cases in which a malicious intent is suspected (e.g., child abuse or neglect) should be referred to an emergency department **(Grade D)**.
2. In patients without evidence of self-harm, abuse, or malicious intent, poison center personnel should elicit additional information including the time of the ingestion, the precise dose ingested, and the presence of co-ingestants **(Grade D)**.
3. Patients who are chronically taking a monoamine oxidase inhibitor and who have ingested any amount of methylphenidate require referral to an emergency department **(Grade D)**.
4. Patients experiencing any changes in behavior other than mild stimulation or agitation should be referred to an emergency department. Examples of moderate to severe symptoms that warrant referral include moderate-to-severe agitation, hallucinations, abnormal muscle movements, headache, chest pain, loss of consciousness, or convulsions **(Grade D)**.
5. For patients referred to an emergency department, transportation via ambulance should be considered based on several factors including the condition of the patient and the length of time it will take for the patient to arrive at the emergency department **(Grade D)**.
6. If the patient has no symptoms, and more than 3 hours have elapsed between the time of ingestion and the call to the poison center, referral to an emergency department is not recommended **(Grade D)**.
7. Patients with acute or acute-on-chronic ingestions of less than a toxic dose (see recommendations 8, 9, and 10) or chronic exposures to methylphenidate with no or mild symptoms can be observed at home with instructions to call the poison center back if symptoms develop or worsen. For acute-on-chronic ingestions, the caller should be instructed not to administer methylphenidate to the patient for the next 24 hours. The poison center should consider making a follow-up call at approximately 3 hours after ingestion **(Grade D)**.
8. Patients who ingest more than 2 mg/kg or 60 mg, whichever is less, of an immediate-release formulation (or the equivalent amount of a modified-release formulation that has been chewed) should be referred to an emergency department **(Grade C)**.
9. If a patch has been swallowed, consider the entire contents of the patch (not just the labeled dose of the patch) to have been ingested. Patients who ingest more than 2 mg/kg or 60 mg, whichever is less should be referred to an emergency department. If it is known that the patch has been chewed only

briefly, and the patch remains intact, significant toxicity is unlikely and emergency department referral is not necessary **(Grade D)**.

10. Patients who ingest more than 4 mg/kg or 120 mg, whichever is less, of an intact modified release formulation should be referred to an emergency department **(Grade D)**.
11. For oral exposures, do not induce emesis **(Grade D)**.
12. Pre-hospital activated charcoal administration, if available, should only be carried out by health professionals and only if no contraindications are present. Do not delay transportation in order to administer activate charcoal **(Grade D)**.
13. Benzodiazepines can be administered by emergency medical services (EMS) personnel if agitation, dystonia, or convulsions are present and if authorized by EMS medical direction expressed by written treatment protocol or policy or direct medical oversight **(Grade C)**.
14. Standard advanced cardiac life support (ACLS) measures should be administered by EMS personnel if respiratory arrest, cardiac dysrhythmias, or cardiac arrest are present and if authorized by EMS medical direction expressed by written treatment protocol or policy or direct medical oversight (**Grade C)**.

Definitions:

Grades of Recommendation and Levels of Evidence

Grade of Recommendation	Level of Evidence	Description of Study Design
A	1a	Systematic review (with homogeneity) of randomized clinical trials
	1b	Individual randomized clinical trials (with narrow confidence interval)
	1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.)
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality randomized clinical trial)
	2c	"Outcomes" research
	3a	Systemic review (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case series, single case reports (and poor quality cohort and case control studies)
D	5	Expert opinion without explicit critical appraisal or based on physiology or bench research
Z	6	Abstracts

CLINICAL ALGORITHM(S)

An algorithm is provided in Appendix 4 of the original guideline document for triage for methylphenidate poisoning.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate out-of-hospital triage and initial out-of-hospital management of patients with suspected methylphenidate poisoning

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline was developed for the conditions prevalent in the United States. While the toxicity of methylphenidate is not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much different. This guideline should not be extrapolated to other settings unless it has been determined that the conditions assumed in this guideline are present.
- This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care, considering all of the circumstances involved. This guideline does not substitute for clinical judgment.

Limitations of the Literature

A major limitation is the paucity of information. Information available to determine a mg/kg toxic dose of methylphenidate following oral exposures is limited to five chart review studies conducted at poison centers (three published and two in abstract form only) and one case report. With the exception of one prospective case series, all of the case series were retrospective chart reviews; conclusions could be incorrect due to missing information. The possibility of inaccurate histories provided to poison centers must always be considered. As with the majority of studies reviewing cases of reported toxic ingestions, doses ingested cannot be confirmed. Three of the five case series included intentional exposures (self-harm and abuse); for these cases, confirming the accuracy of the

reported dose ingested is even more problematic. An additional limitation is that the studies, with one exception, did not separate patients who received gastrointestinal decontamination and, therefore, it is unknown whether decontamination had an effect. None of the three level 4 case series was specifically intended to determine the mg/kg toxic dose of methylphenidate. While mean mg/kg ingested doses were calculated (some of the studies did not differentiate between immediate release [IR], sustained release [SR], and extended release [ER] formulations, and one of the case series did not differentiate between IR, SR, ER, controlled- release osmotic pressure delivery system [OROS], controlled delivery [CD], and long-acting [LA] formulations), the primary purpose of these studies was to profile methylphenidate exposure demographics and outcomes. Therefore, symptoms were presented as numbers of patients having symptoms or the percentage of patients having a given symptom. Consequently, determining which specific symptoms were associated with any mg/kg dosage range was not possible. In one of the three case series and one of the two abstracts, it was not possible to separate the mg/kg toxic doses between those less than 6 years of age and those 6 years of age and older. This limits the ability to determine if there is a threshold dose at which toxicity is likely to occur. With the exception of a statement in an abstract that hyperactivity and dilated pupils were noted in the two patients who reportedly ingested 1 to 2 mg/kg, none of the published reports provided a description of the adverse effects associate with a given mg/kg dose reported. All that was reported was the total number or the percentage of patients who developed a specific symptom. This is problematic when trying to use the data to make decisions on home management, because one is not able to determine from the data how many children or adults developed symptoms not appropriate for home observation at a given mg/kg ingested dose.

Another limitation of the literature is the lack of toxic dose information for the CD, OROS, and LA formulations of methylphenidate. With the exception of one abstract and one case series, the studies were conducted during years in which the CD, OROS, and LA formulations were not on the market. In one level 4 report, the mean mg/kg doses reported did not differentiate between IR, SR, ER, OROS, CD, or LA formulations. This leaves one abstract as the only information available on the toxic dose of modified-release formulations. For the 152 CD, OROS, and LA ingestions described in this abstract, outcomes were only described for 57 cases in which double doses had been taken. Mean doses for all three products (CD, OROS, and LA) were combined into one mean mg/kg dose despite the different release rates of these formulations.

Information on the toxic dose of the SR and ER formulations of methylphenidate are confined to one abstract in which 38 ingestions of SR or ER products were reported; however, only 11 were treated with observation alone. Two other reports did not differentiate mean mg/kg toxic doses between the immediate-release formulations and the SR or ER formulations. Another report only included ingestions of immediate-release products.

There are no data on the consequences of methylphenidate patch ingestion. It is unknown how chewing the patch would affect drug delivery.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Scharman EJ, Erdman AR, Cobaugh DJ, Olson KR, Woolf AD, Caravati EM, Chyka PA, Booze LL, Manoguerra AS, Nelson LS, Christianson G, Troutman WG, American Association of Poison Control Centers. Methylphenidate poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2007 Oct-Nov;45(7):737-52. [80 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Feb 9

GUIDELINE DEVELOPER(S)

American Association of Poison Control Centers - Professional Association

SOURCE(S) OF FUNDING

Health Resources and Services Administration, U.S. Department of Health and Human Services

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Booze's husband is employed by AstraZeneca.

Dr. Erdman was employed by AstraZeneca during his contribution to the development of this guideline.

There are no other potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Poison Control Centers.

Print copies: Available from the American Association of Poison Control Centers, 3201 New Mexico Avenue NW, Suite 330, Washington, DC 20016

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on December 18, 2007. The information was verified by the guideline developer on January 14, 2008.

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